

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001817

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C12N 15/54, C12Q 1/48, C12N 9/10, C07K 14/47, C07D 209/14
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C12N, C12Q, C07K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, EPODOC, WPI, MEDLINE, EMBASE, STN-CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Biochemical Pharmacology, Volume 25, 1976, Roy A. Henry et al, "Inhibition of glutathione-S- aryltransferase from rat liver by organogermanium, lead and tin compounds", pages 2291-2295, page 2292, Results --	1-8,15-20
X	JBC Papers in Press. Published on February 28, 2002 as Manuscript M201062200, Copyright 2002 by the American Society of Biochemistry and Molecular Biology, Ann-Sofie Johansson and Bengt Mannervik, "Active-Site Residues Governing High Steroid Isomerase Activity in Human Glutathione Transferase A3-3", pages 1-35, Figure 1 --	1-8,15-20

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

- * Special categories of cited documents
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

6 February 2004

Date of mailing of the international search report

25-03-2004

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **21-24**
because they relate to subject matter not required to be searched by this Authority, namely:
see extra sheet
2. ☒ Claims Nos.: **11-14 and part of 1-6, 15-20**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see extra sheet
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
7-8 and part of 1-6, 15

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

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Box II.1

Claims 21-24 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for those claims. The search has been based on the alleged effects of the compounds or medicaments.

Box II.2

Claims 1-5

Glutathione S-transferases (GSTs; EC 2.5.1.18) are ubiquitous multifunctional enzymes which play a key role in cellular detoxification. Based on their sequence homology, substrate specificity and immunological cross-reactivity, GSTs have been grouped into five species-independent classes of isoenzymes. Four of these classes (alpha, pi, mu and theta) comprise cytosolic enzymes, a fifth rather distinct form is microsomal. All cytosolic GSTs are found to be homo- or hetero- dimeric enzymes (from within the same class) with a relative molecular weight of ca. 50 kDa. (Krengel et al. (1998). FEBS Lett. 422, 285-290.)

Present claims 1-5 relate to a method of screening for compounds, wherein a glutathione transferase (GST) is used as a drug target. The method is only defined by reference to the following parameters:

- P1: The compound suppress the concentration of active GST or,
- P2: The compound inhibits the steroid isomerase activity of GST.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. Methods of screening in similar manners are described in Hiratsuka et al (Biochem J-2001-(355), 237-234) for GST isoforms.

Methods of screening GST enzymes are known even in documents: WO 00/18937A1 and US6063570.

The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to:

The parts relating to the methods mentioned in the description on pages 5-7 (Table 1).

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Claim 6

Present claims 6 relates to an extremely large number of possible compounds.

The expressions: "homologs" or "other chemical ligands" or "similar electrophilic atoms"; may influence the active compound in different ways. If such expressions influence the activity of the compound, it must be evident from the claim what groups are involved. In this case, claim 6 lacks definition of matter, which according to Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the variations claimed (See Table 1, description).

Claims 11-14 and part of 15-20

The information given in the working examples of the description is not considered to fulfil the requirements of exemplification in such a way that the claims are sufficiently supported (Articles 5 and 6 PCT Rules).

Consequently the search has been carried out for those parts of the claims, which appears to be supported, and disclosed, namely those parts related to the methods mentioned in the description on pages 5-7 (Table 1).

Box III

According to Article 17(2 and 3) and Rule 13.2 PCT, an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i. e. features that define a contribution which each of the inventions makes over the prior art. The present application relates to inhibitors of GST, according to the following two inventions, namely:

- 1- An inhibitor of GST with the formula I, wherein X=Sn according to claims 7-8 and part of 1-6,15.
- 2- An inhibitor of GST, wherein the inhibitor is a steroid according to claims 9-10 and part of 1-6,15-20.

Inhibitors of GST are known according to D1 (W09632936A2). D1 relates to novel haloenol lactone compounds as inhibitors of GST. The compounds of D1 are useful for the specific measurement of particular isoenzymes of glutathione S-transferase and for the treatment of drug resistance in cancer. Thus, no special technical feature links inventions 1 and 2. The application is therefore not considered to fulfil the requirements of Rule 13.2 (Art 17.3) PCT.

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Invention 1 has been searched to the extend it was possible, based on the exemplified IC-50 measure of table 1 in the description.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Biol. Chem. Vol. 276, Issue 35, August 31, 2001, Ann-Sofie Johansson and Bengt Mannervik, "Human Glutathione Transferase A3-3, A Highly Efficient Catalyst of Double-bond Isomerization in the Biosynthetic Pathway of Steroid Hormones", pages 33061-33065, Results, http://www.jbc.org/cgi/content/full/276/35/33061 --	1-8,15-20
Y	Biochem. J., Volume 360, 2001, David Sheehan et al, "Structure, function and evolution of glutathione transferases: implications for classification of non-mammalian members of an ancient enzyme superfamily", pages 1-16, Conclusions --	1-8,15-20
Y	Biochem. J., Volume 355, 2001, Akira Hiratsuka et al, "(S)-Preferential detoxification of 4-hydroxy-2(E)-nonenal enantiomers by hepatic glutathione S-transferase isoforms in guinea-pigs and rats", pages 237-244, Tables 1-3 --	1-8,15-20
A	WO 9520601 A1 (THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL), 3 August 1995 (03.08.1995), page 29 - line 34 --	1-8,15-20
A	WO 0018937 A1 (E.I DU PONT DE NEMOURS AND COMPANY), 6 April 2000 (06.04.2000), claim 13 --	1-8,15-20
A	US 6063570 A (MCGONIGLE ET AL), 16 May 2000 (16.05.2000), claims 7,8,9 --	1-8,15-20
A	FEBS Letter, Volume 422, 1998, Krengel et al, "Glutathion S-transferase (GSTA4-4), pages 285-290, abstract http://www.csb.gu.se/ute/projects/gst.html --	1-8,15-20

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 9632936 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA), 24 October 1996 (24.10.1996), claim 29</p> <p style="text-align: center;">-- -----</p>	1-8,15-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/02/2004

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WO	9520601	A1	03/08/1995	AU	1738395 A	15/08/1995
				CA	2155185 A,C	18/08/1994
				EP	0689590 A	03/01/1996
				JP	3210342 B	17/09/2001
				JP	8506487 T	16/07/1996
				SG	55153 A	21/12/1998
				US	5747334 A	05/05/1998
				US	5948635 A	07/09/1999
				WO	9418318 A	18/08/1994
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WO	0018937	A1	06/04/2000	AU	1063899 A	17/04/2000
				CA	2339349 A	06/04/2000
				EP	1117810 A	25/07/2001
				US	2003032030 A	13/02/2003
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US	6063570	A	16/05/2000	US	6168954 B	02/01/2001
				US	6171839 B	09/01/2001
<hr/>						
WO	9632936	A1	24/10/1996	US	5767147 A	16/06/1998
				US	6103665 A	15/08/2000
				US	6495370 B	17/12/2002